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# In vitro characterization of microcontainers as an oral drug delivery system

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## ABSTRACT SUMMARY

We here present *in vitro* studies showing the promise of microcontainers (fabricated in either SU-8 or Poly(lactic acid) (PLLA)) as an oral drug delivery system for the poorly water-soluble drug, furosemide.

## INTRODUCTION

Micro fabricated drug delivery devices have been proposed as an approach for delivering drugs orally as they can protect the drug through the stomach and thereby, possibly improve the oral bioavailability[1,2]. Microcontainers are polymeric devices consisting of a flat base with a walled reservoir[2,3]. The microcontainers are characterized by enabling unidirectional release directly to the intestinal mucosa, as only one side of the microcontainers is open. The cavity of the microcontainers is filled with drug and subsequently, coated with a lid of a pH-sensitive polymer to protect the drug from degradation and premature release in the stomach. After emptying into the duodenum, the polymer lid will dissolve at the higher pH in the small intestine and the drug is released and absorbed through the intestinal wall (Figure 1).

The purpose of this study was to *in vitro* characterize the microcontainers as an innovative oral drug delivery system for the poorly water-soluble drug, furosemide.

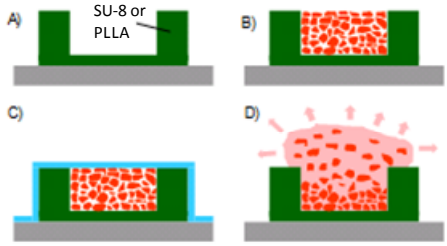


Figure 1. A) Fabrication of microcontainers in either SU-8 or PLLA. B) Filling with amorphous furosemide salt. C) Spray coating of a lid of Eudragit L100. D) Dissolution of coating and release of drug.

## EXPERIMENTAL METHODS

Prototype microcontainers with inner diameters of 230 µm were fabricated using epoxy resins (SU-8, Microchem, USA) patterned through two steps of photolithography defining the bottom and the walls of the microcontainers (Figure 2A). Alternatively, biodegradable microcontainers were prepared in (PLLA) by using the technique of hot embossing (Figure 2B).

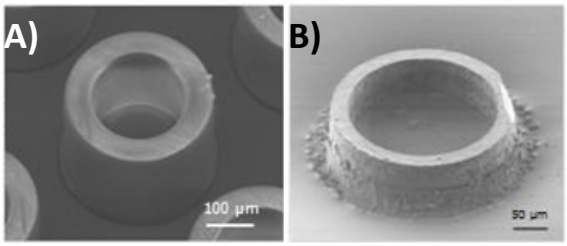


Figure 2. Microcontainers fabricated by A) UV patterning of SU-8 and B) hot embossing in PLLA.

The microcontainers were filled with amorphous furosemide sodium salt (prepared by spray drying[4]) followed by spray coated (ExactaCoat, Sono-Tek, USA) with a solution of 1 wt% Eudragit L100 (Evonik Industries, Essen, Germany). The release of the drug from the microcontainers was evaluated in a biorelevant gastric medium at pH 1.6 and biorelevant intestinal medium at pH 6.5. The intestinal permeability of the amorphous furosemide salt loaded into the microcontainers was evaluated using the Caco-2 cell model with biorelevant intestinal medium pH 6.5 as the apical medium.

## RESULTS AND DISCUSSION

After filling of the microcontainers with amorphous furosemide salt (Figure 3a), the cavity of the drug-filled microcontainers were spray coated with Eudragit L100, resulting in a 7 µm thick Eudragit layer (Figure 3b).

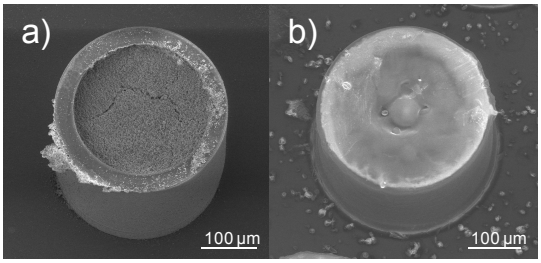


Figure 3. SEM image of a microcontainer a) filled with amorphous furosemide salt. b) filled with drug and subsequently coated with 7 µm Eudragit L100.

From the release experiments, it was observed that the Eudragit layer prevented drug release in gastric medium, while an immediate release of the amorphous furosemide salt was seen in the intestinal medium (Figure 4).

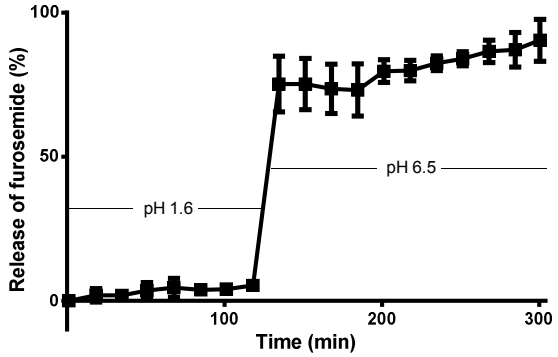


Figure 4. Release profiles from microcontainers filled with amorphous furosemide salt and coated with Eudragit L100 in gastric medium pH 1.6 and intestinal medium pH 6.5. Data shown represent the mean of 3 replicates±SD.

The permeability studies showed a fast absorption of the amorphous furosemide salt with no significant difference between the microcontainers ($P_{app}$ $1.79 \cdot 10^{-5} \pm 0.68 \cdot 10^{-6}$ cm/s, mean±SD n=11) and bulk powder of amorphous furosemide salt ($P_{app}$ $1.62 \cdot 10^{-5} \pm 1.039 \cdot 10^{-5}$ cm/s, mean±SD n=11) (Figure 5).

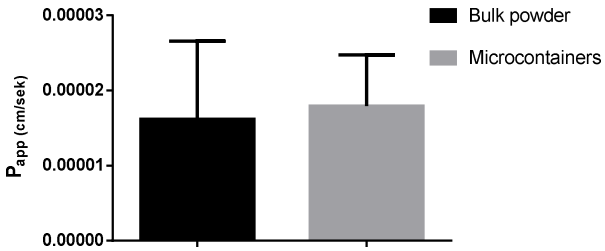


Figure 5. The intestinal permeability through Caco-2 cells of the amorphous furosemide salt in bulk form and loaded into microcontainers. Data shown represent the mean of 11 replicates±SD.

## CONCLUSION

Microcontainers were successfully fabricated and loaded with powder drug. The Eudragit layer prevented drug release in gastric medium, and facilitated an immediate release in the intestinal medium. Furthermore, the amorphous furosemide salt loaded in microcontainers was fast absorbed through the Caco-2 cell monolayer. Microcontainers therefore show considerable future potential as oral drug delivery systems.

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